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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,686	06/30/2005	Evert Johannes Bunschoten	0470-045923	3094

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EXAMINER	
CHUI, MEI PING	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,686	BUNSCHOTEN ET AL.	
	Examiner	Art Unit	
	MEI-PING CHUI	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-33* is/are pending in the application.

4a) Of the above claim(s) *29-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *N/A*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Action

Receipt of Amendments/Remarks filed on 12/10/2007 is acknowledged. Claims 1-17 are cancelled and claims 18-33 are pending in the application. Claim 18 has been amended. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, **THIS ACTION IS MADE FINAL.**

Status of Claims

Accordingly, claims 18-28 are presented for examination on the merits for patentability as they read upon the elected subject matter and claims 29-33 directed to non-elected invention(s) are withdrawn.

Withdrawn claim rejections

(1) The previous rejection over **claims 18-28**, under 35 U.S.C. 112 second paragraph as being indefinite, are withdrawn in light of the amendment filed on 12/10/2007.

(2) The previous rejection over **claims 18-28**, under 35 U.S.C. 112 first paragraph as failing to comply with the enablement requirement, are withdrawn in light of the amendment filed on 12/10/2007.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

The rejection over **claims 18-28**, under 35 U.S.C. 103(a) as being unpatentable over Voskuhl, R. R. (U.S. Patent Application Publication No. 2002/0183299) in view of Spicer et al. (U. S. Patent No. 5,340,584), is maintained.

Response to Arguments

Applicant argues that the instantly claimed estrogen, estetrol, is a much less potent estrogen than the natural estrogens estradiol and estriol, as taught by Voskuhl, R. R. (see Remarks: page 11, second paragraph).

Applicant's arguments filed on 12/10/2007 have been fully considered but they are not persuasive. Although available knowledge shows the estrogenic potency of estetrol (E4) is lower than other natural estrogens, i.e. estradiol (E2) or estriol (E3), for example; it does not mean that estriol (E3) is ineffective as an estrogenic compound compared to estetrol (E4). The prior art can be modified or combined to rejected claims as *prima facie* obvious as long as there is a reasonable expectation of success. Applicant is required to provide evidence showing there was no reasonable expectation of success may support a conclusion of obviousness (see MPEP 716.01 and 2143.02).

Furthermore, Applicant argues that one having ordinary skill in the art would not be motivated to combine the teachings of Voskuhl, R. R. with those of Spicer et al. since these references related to very different fields (autoimmune diseases verses contraception and gynecological disorders), and thus provides little guidance for alternative estrogenic agents besides those explicitly mentioned in Voskuhl, R. R. (see Remarks: page 12, third paragraph).

Applicant's arguments filed on 12/10/2007 have been fully considered but they are not persuasive. Voskuhl, R. R. teaches a method of treating autoimmune related disease, more

specifically, Th-1 mediated autoimmune disease such as multiple sclerosis (page 8, claims 2-3), by administering a steroid hormone, such as an estrogen as the primary therapeutic agent, to mammals (page 2, paragraph 0023, line 1-5). Voskuhl, R. R. further teaches that said steroid hormone is preferably an estrogen, or its metabolite, that has a similar core steroidal structure to the natural estrogens, namely, estrone, estriol and estriol, and may have one or more hydroxyl functional group at one or more ring positions (page 3, paragraph 0039, line 1-4) compared to said estrogens.

The goal of the primary reference, namely Voskuhl, R. R., is to utilize an estrogen, i.e. estriol, or its metabolite or derivative, in a method of treating autoimmune related disease, i.e. multiple sclerosis. Thus, the suggestion by Voskuhl, R. R. has demonstrated the importance of the steroidal core structure in the method of treating autoimmune related disease. Voskuhl, R. R. further suggests that the metabolite(s) of said estrogen, such as those have one or more hydroxyl functionality at one of the ring, are also suitable to use.

The goal of the secondary reference, namely Spicer et al., is to demonstrate that estriol (the estrogen taught by Voskuhl, R. R.) and the instantly claimed estetrol both have the identical steroidal core structure with identical hydroxyl function groups at C3, C16 and C17 positions. Thus, they are from the same class of estrogens, as suggested by Voskuhl, R. R., in which the estetrol has an additional hydroxyl group at C15 (or R_5 in the instant estrogenic formula) of D-ring position and has the same steroidal skeleton configuration 8β, 9α, 13β and 14α-positions.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because the combined teachings of the prior art fairly suggests the instant claims, as evidenced by the references,

especially in the absence of evidence to the contrary. Applicant is required to provide evidence showing any unexpected results (see MPEP 2114.06(II)).

It is noted that claim 18 has been amended to a method of treating or prophylactically treating an immune mediated disorder …" (see Remarks: page 8, third paragraph and claim 18 of Amendments filed on 12/19/2007). The term "prophylactically" is "a preventive measure" that is designed and used "to prevent a disease from occurring" (see Prophylactic definition - Medical Dictionary of Popular Medical Terms: retrieved on 03/14/2008 via www.medterms.com/script/main/art.asp?articlekey=11902). Since the term "prophylactic" is defined the same as "preventive"; therefore, it is the Examiner's position that claims 18-28 are still construed to be directing to a method of "treating" or "preventing" an immune mediated disorder in a mammal as claimed.

NEW GROUND(S) OF CLAIM REJECTIONS

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement of the Invention

Claims 18-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 18-28 while being enabling for treating an immune mediated disease selected from the group consisting of multiple sclerosis, rheumatoid arthritis, osteoarthritis, as claimed in claim 18, comprising the administration of a therapeutically effective amount of an estrogenic component of said formula, does not reasonably provide enablement for prophylactically treating an immune mediated disease in aforementioned method due to the diverse origination and causes of said disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

An analysis of whether the scope of a particular claim(s) is actually supported by the disclosure in a patent application requires a determination of whether the disclosure, at the time of filing, contained sufficient information regarding the subject matter of the claim at issue so as to enable one skilled in the pertained art to use the claimed invention without undue experimentation. *In re Wands*, 8 USPQ 2d 140 (Fed. Cir. 1988). Therefore, the test of enablement is not whether experimentation is necessary, but rather, if experimentation is in fact

necessary, whether it is reasonably considered to be undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Determining the issue of enablement with respect to a claim is a question of law based on underlying factual findings. *In re Vaeck*, 20 USPQ 2d, 1444 (Fed. Cir. 1991). More particularly, there are many factors to be considered in determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and whether any necessary experimentation is reasonably considered to be "undue". See *In re Wands* at page 1404. MPEP § 2164.01(a). The court in *In re Wands* set forth the following factors to be considered, which included, without limitation, the: 1). scope or breadth of the claims; 2). nature of the invention; 3). relative level of skill possessed by one of ordinary skill in the art; 4). state of, or the amount of knowledge in, the prior art; 5). level or degree of predictability, or a lack thereof, in the art; 6). amount of guidance or direction provided by the inventor; 7). presence or absence of working examples; and 8). quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Scope or breadth of the claims:

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, the prophylactically treating of immune mediated disorders which are developed from multiple origins and causes. However, Applicant is claiming utilizing one said estrogenic compound in said method can effectively treat an immune mediated disorder in a

mammal, or can prophylactically treating said immune mediated disorder from occurrence, even though these diseases are very different in their multitude of development and their origination, implicitly include all causes and factors that give rise to such disorder can be treated or prophylactically treated by administering said single estrogenic compound.

Nature of the invention:

The nature of the invention is directed to a method of treating or prophylactically treating an immune mediated disorder in a mammal, such as multiple sclerosis, rheumatoid arthritis and osteoarthritis, by administering a therapeutically effective amount of an estrogenic compound to said mammal.

State of or the amount of knowledge in the prior art:

It is known in the art that the cause of multiple sclerosis is unknown and researchers are still not sure what triggers an attack to patients with multiple sclerosis except there appears to be a genetic link to this disease (see MedlinePlus Medical Encyclopedia: Multiple Sclerosis, retrieved on 03/28/2008 via www.nlm.nih.gov/medlineplus/ency/article/000737.htm, dated on 08/06/2007, Page 1 and 2). It is also known that multiple sclerosis appears to affect woman more than man, and people with a family of multiple sclerosis and those who live in a geographical area with a higher incidence rate for multiple sclerosis have a higher risk of the disease (MedlinePlus Medical Encyclopedia: Multiple Sclerosis, retrieved on 03/28/2008, page

2; also see WebMD: Multiple Sclerosis – Prevention, retrieved on 03/28/2008 via www.webmd.com/multiple-sclerosis/tc/multiple-sclerosis-ms-prevention, dated on 03/23/2006).

In addition, the state of art(s) also recognize that, as of current, there is no known method to prophylactically treat rheumatoid arthritis because the exact cause of the disease is not known, and factors, such as infection, genes and hormones level, are speculated to contribute to this disease (see MedlinePlus Medical Encyclopedia: rheumatoid arthritis, retrieved on 03/28/2008 via www.nlm.nih.gov/medlineplus/ency/article/000431.htm, dated on 07/27/2007, page 1-2 and 4; also WebMD: Rheumatoid Arthritis – Prevention, retrieved on 03/28/2008 via www.webmd.com/rheumatoid-arthritis/tc/rheumatoid-arthritis-prevention, dated on 08/23/2006).

Therefore, currently there is no known method that can cure or truly prophylactically treat the immune mediated diseases, i.e. multiple sclerosis and rheumatoid arthritis, by employing a single therapeutic estrogen because the causes of these diseases are still unknown and derived from diverse factors.

Amount of guidance or direction provided by the inventor:

Although the instant specification discloses that said estrogenic component, such as estetrol, treats an immune mediated disorder, it remains silent on the prophylactic treatment of the immune mediated disorders, i.e. multiple sclerosis or rheumatoid arthritis, which may be caused by genetic or unknown promoting factors.

Presence or absence of working examples:

The specification provides some scientific data and working embodiments with respect to the administration of estetrol for treating multiple sclerosis and arthritis. However, in the specification, there is no example(s) of the administration of estetrol for prophylactically treating multiple sclerosis or arthritis as claimed in the instant invention.

Level or degree of predictability, or a lack thereof, in the art:

A high degree of unpredictability exists in the state of the art regarding how to prophylactically treat multiple sclerosis or rheumatoid arthritis. Risk factors evaluation, although, may help to avoid the chances of further developing such immune mediated disorder, but at this stage of the art, many of them are still unknown and cannot be controlled, such as the factor due to the potential of weak immune system or the gene that one inherits from their parents.

Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure:

One of ordinary skill in the art would be required to conduct an undue amount of experimentation to reasonably and accurately determine whether said estrogenic compound and corresponding method of the instant application does in fact effectively and prophylactically treat all the claimed immune mediated disorders in the instant invention.

In conclusion, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the prophylactically treating an immune mediated disorder utilizing an estrogenic agent, is not enabled because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28, which is depended on claim 18, recites the immune mediated disorder is selected from multiple sclerosis, rheumatoid arthritis, osteoarthritis, insulin dependent diabetes (type I diabetes), systemic lupus erythrematosis and psoriasis. Since claim 18 recites the limitation of the immune mediated disorder, which is selected from the group "consisting of"

multiple sclerosis, rheumatoid arthritis and osteoarthritis; therefore, the dependent claim 28 is also limited to these three diseases only.

Conclusion

No claims are allowed. Applicant's amendment filed and adding new claims necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sharmila Gollamudi Landau/

Primary Examiner, Art Unit 1611